REMARKS/ARGUMENTS

Claims 1-9, 13-19 and 21-22 are active. Claims 10-12 and 20 have been withdrawn from consideration. Claims 21-22 track claim 1 and also find support on pages 5-7 of the specification. No new matter has been introduced. The Applicants thank Examiner Saoud for considering their prior arguments and withdrawing the prior grounds of rejection. The new grounds of rejection are addressed below. Favorable consideration of these arguments and allowance of this application are respectfully requested.

Restriction/Election

The Applicants previously elected without traverse **Group I**, claims 1-9 and 12, directed to methods of using a protein (e.g., a prolactin variant). The Applicants respectfully request that the claims of the nonelected group(s) or claims directed to any other withdrawn subject matter which depend from or otherwise include all the limitations of an allowed elected claim, be rejoined upon an indication of allowability for the elected claim, see MPEP 821.04.

Rejection—35 U.S.C. §103(a)

Claims 1-9 and 13-19 were rejected under 35 U.S.C. §103(a) as being unpatentable over Goffin, et al., J. Biol. Chem. 271:16573, in view of Bernichtein, et al., Endocrine Soc., 82nd Annu. Meeting, Abstract 613. The Applicants respectfully traverse this rejection because the prior did not suggest or provide a reasonable expectation of success for the combination of mutations required by the invention. Specifically, it did not suggest that selection of the required combination of mutations would provide a superior antagonist with no undesirable residual agonist activity. As discussed in detail below, the closest prior art antagonists have residual (e.g., for Goffin's G129R), or even enhanced or more potent (e.g.,

for Bernichtein's mutants with N-terminal deletions), agonist activity. Experimental data support the role of prolactin in promoting various tumor-promoting actions (specification, bottom of page 1). Prolactin antagonists would block such tumor-promoting activity, by antagonizing such tumor-promoting action. Residual agonist activity would negate anti-tumor effects of a pure antagonist (specification, top of page 4).

Goffin was relied upon for describing human prolactin (hPRL) antagonists containing a substitution of glycine 129 in wild-type prolactin with arginine (G129R). This substitution occurs within site 2 of wild-type prolactin; the last paragraph on page 3 of the OA indicates that it results in "antagonism of binding to the receptor at site 2". However, the OA acknowledges that Goffin did not disclose modification of the N-terminus of wild-type prolactin, nor did it provide a reasonable expectation of success for antagonists with no residual agonist activity. Unlike the antagonists of the invention, the G129R mutant has residual agonist activity as evident from Figs. 6 and 8 of the specification.

Page 4 of the OA indicates that Bernichtein "suggests that antagonistic properties of site 2 analogs could be enhanced if paired with a deletion of **residues 10-14**, which increases site 1 affinity". Bernichtein teach N-terminal deletions of human prolactin and indicate that deletion of the 9 N-terminal residues increased site 1 affinity, while deletion of the 14 N-terminal residues resulted in a decrease of affinity. Bernichtein suggests that antagonistic properties of site 2 analogs could be enhanced if paired with a deletion of residues 1-9, which increases site I affinity (but not with a deletion of residues 1-14, which decreases the affinity). However, it did not suggest that such a pairing would provide antagonists without residual agonist activity.

In distinction, the analogues of the invention (whether to have a deletion of residues 1-3, or a longer deletion up to residue 14) do not have better antagonistic properties than site 2 analogs of the prior art such as, but, surprisingly, are devoid of the residual agonist activity

which made prior art site 2 analogs unsuitable for *in vivo* use for reasons discussed in the section bridging pages 3 and 4 of the specification.

This shown by the *in vitro* and *in vivo* comparisons between the prior art analog G129R and the analogs of the invention provided in the present disclosure. Actually, the antagonistic activity of the analogues of the invention, tested using the transcriptional *in vivo* bioassay used by both Bernichtein and Goffin (page 18 lines 21-27 and Figure 7B), and another *in vitro* bioassay (page 19 lines 13-34 and Figure 8B), is not higher than, but similar to the antagonistic activity of the analogues of Goffin. In contrast, the prior art analog G129R has a residual agonist activity which is not shown by the analogs of the invention (*cf.* page 17, line 25 to 18, line 9, and Figure 6; page 18, line 29 to 19, line 11, and Figure 8A); Example 4 and Figure 9; Example 6 and Figure 11).

Moreover, one of ordinary skill in the art following the suggestions of Bernichtein to combine the two types of mutations to obtain a more potent hPRL antagonist would have first logically tested the molecules for their affinity for PRLR (since Bernichtein suggests that the enhanced antagonistic properties should result from an increased site 1 affinity), and secondly for their antagonistic properties.

In testing the affinity of the molecules for PRLR, the ordinary artisan would have found that the N-terminal deletion does not increase the affinity of site 2 analogs (*cf.* page 13 lines 6-18 of the instant application). Serious doubt would have resulted that an improvement of the antagonistic properties was to be expected, and would have discarded the suggestion of Bernichtein. Accordingly, following the suggestion of the prior art would not have provided a reasonable expectation of success for the invention.

Assuming, *arguendo*, that one of skill in the art would have nevertheless undertaken to test the molecules for their antagonistic properties, he would have used for this the transcriptional *in vivo* bioassay which is disclosed by Bernichtein as the more suitable

method for analyzing hPRL/hPRLR interaction, and which previously allowed to Goffin to discover the antagonistic properties of site 2 analogs, which were undetectable using the classical Nb2 assay (cf. for instance Goffin, page 16573, end of 2nd column). Doing this, one of skill in the art would, have found that no enhancement of the antagonistic properties resulted from the combination of the two types of mutations. Thus, the prior art did not provide a reasonable expectation of success for the invention, because following the teaching of Bernichtein, one of ordinary skill in the art would have considered that the combination of N-terminally deletions with site 2 mutations was of no use, and would have discarded this approach.

Therefore, this rejection cannot be sustained, because the prior art did not disclose, suggest or provide a reasonable expectation of success for the present invention.

Conclusion

In view of the amendments and remarks above, the Applicants respectfully submit that this application is now in condition for allowance. An early notice to that effect is earnestly solicited.

Respectfully submitted,

OBLON, SPIVAK, McCLELLAND,
MAIER & NEUSTADT, P.C.
Norman F. Oblon

Thomas M. Cunningham, Ph.D.
Attorney of Record
Registration No. 45,394

Customer Number
22850

Tel: (703) 413-3000
Fax: (703) 413 -2220
(OSMMN 08/07)